

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION (PCT Rule 61.2)

Date of mailing (day/month/year)
06 April 1999 (06.04.99)

To:
United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

International application No.
PCT/US98/10685

Applicant's or agent's file reference
75844

International filing date (day/month/year)
27 May 1998 (27.05.98)

Priority date (day/month/year)
27 May 1997 (27.05.97)

Applicant

MITCHELL, James, B. et al

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

18 December 1998 (18.12.98)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Sean Taylor

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

REC'D 15 OCT 1999

PCT

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

18

| | | |
|---|--|---|
| Applicant's or agent's file reference 75844 | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/US98/10685 | International filing date (day/month/year) 27/05/1998 | Priority date (day/month/year) 27/05/1997 |
| International Patent Classification (IPC) or national classification and IPC A61K33/00 | | |
| Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA, re .. . | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 18/12/1998 | Date of completion of this report 13. 10. 99 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Isert, B Telephone No. +49 89 2399 8691 |
|   | |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/10685

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

| | | | |
|--------|---------------------|---------------------------|------------|
| 1,3-17 | as originally filed | | |
| 2 | as received on | 20/08/1999 with letter of | 20/08/1999 |

Claims, No.:

| | |
|------|---------------------|
| 1-27 | as originally filed |
|------|---------------------|

Drawings, sheets:

| | |
|---------|---------------------|
| 1/2,2/2 | as originally filed |
|---------|---------------------|

2. The amendments have resulted in the cancellation of:

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.
 claims Nos. 1-27 in part.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/10685

because:

- the said international application, or the said claims Nos. 1-27 (for industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. 1-27 in part.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | |
|-------------------------------|------------------|
| Novelty (N) | Yes: Claims 1-27 |
| | No: Claims |
| Inventive step (IS) | Yes: Claims |
| | No: Claims 1-27 |
| Industrial applicability (IA) | Yes: Claims 1-27 |
| | No: Claims |

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

s e separate sh t

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/10685

SECTION III

Claims 1-27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V:

- 1). The present report solely concerns the use of the compound Tempol in accordance with the worked examples, and the general idea underlying the application that is the use of nitroxide in the treatment of cancer. See also Box III (Sheets 1-2), and the International search report.

- 2). Prior art

The following documents (D) cited in the International search report are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 = PAACR ANNUAL MEETING, vol. 36, no. 0, 1995, page 387
D2 = PAACR ANNUAL MEETING, vol. 38, no. 0, March 1977, page 193
D3 = PAACR ANNUAL MEETING, vol. 39, no. 0, March 1998, page 90
D4 = WO -A- 96 40127

Unless indicated otherwise reference is made to the relevant passages emphasized in the search report.

- 2.1 D3 is an intermediate document which represents the scientific disclosure of the subject- matter of the present application.

- 3). Novelty:

The subject-matter of the present claims 1-27 is considered novel.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/10685

The claims 1-27 relate to the use of nitroxide or a prodrug thereof in the treatment of cancer. D1 and D2 differ therefrom basically in that they describe cytotoxic effects of the presently preferred piperidine nitroxide Tempol against cancer cells in vitro.

4). Inventive step

The subject-matter of claims 1-27 is not considered inventive:

The present application relates to the prophylactic and therapeutic treatment of cancer in animals.

On the basis of D1 and D2, which show chemotherapeutic efficacy of Tempol in vitro, the problem of the present application could be to identify possible conditions bringing about an anticancer effect in vivo. As shown in the examples of the present application, the development of cancer could be prevented by continuous oral prophylactic administration of Tempol. This particular finding is considered non-obvious from the prior art.

It is noted that the scope of the present claims includes therapeutic cancer treatment as well as various modes/schemes of administration. However, there is no indication in the application which justifies a generalisation of the working examples in this respect. Moreover it appears, that a skilled artisan would expect an anticancer effect of Tempol in vivo, e.g., after administration of high doses, as the prior art does not differentiate between in vitro and in vivo effects of nitroxides, either. See page 2, line 18 - page 3, line 7 of the application.

5). Industrial applicability:

For the assessment of the present claims 1-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/10685

dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VIII

- 6). It is apparently not clear from the description, which cancers originate from a defect of the p53 gene (claims 23,25,27).

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|--|---|--|
| Applicant's or agent's file reference 75844 | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/ US 98/ 10685 | International filing date (day/month/year) 27/05/1998 | (Earliest) Priority Date (day/month/year) 27/05/1997 |
| Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA, re | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **5** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (see Box I).
2. Unity of invention is lacking (see Box II).
3. The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - Transcribed by this Authority
4. With regard to the title, the text is approved as submitted by the applicant.
 the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - the text is approved as submitted by the applicant.
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:

Figure No. _____

 - as suggested by the applicant.
 - because the applicant failed to suggest a figure.
 - because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds, which are defined by the general definition in the claims 1-22, the search had to be restricted for economic reasons. The search was limited to the compound(s) for which pharmacological data was given and to the general idea underlying the application. (see PCT Guidelines, Chapter III, paragraph 2.3 & 3.6).

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/10685

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K33/00 A61K31/395 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| X | MONTI ET AL.: "Cytotoxicity of Tempol, a piperidine nitroxide spin label, against different neoplastic and non-neoplastic cell lines" PAACR ANNUAL MEETING, vol. 36, no. 0, 1995, page 387 XP002075471 * see abstract no. 2304 * | 1-23,25, 27 |
| X | MONTI ET AL.: "DNA damage and apoptosis in human leukemic cells treated with the piperidine nitroxide Tempol" PAACR ANNUAL MEETING, vol. 38, no. 0, March 1997, page 193 XP002075472 * see abstract no. 1298 * | 1-23,25, 27 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 August 1998

Date of mailing of the international search report

11.09.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Isert, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/10685

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| P,X | MONTI ET AL.: "The piperidine nitroxide Tempol induced apoptosis and P21-WAF1-CIP1 expression in P53-deficient cells" PAACR ANNUAL MEETING, vol. 39, no. 0, March 1998, page 90 XP002075475 * see abstract no. 610 * --- | 1-28 |
| A | WO 96 40127 A (US GOVERNMENT) 19 December 1996 * see in particular claims 1-3; page 10, lines 11-19 * ----- | 1-28 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/10685

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|------------------|-------------------------|------------------|
| WO 9640127 A | 19-12-1996 | AU 6102896 A | 30-12-1996 |

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Larcher, Carol
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
CHICAGO, Illinois 60601-6780
ETATS-UNIS D'AMERIQUE

Berky

| | |
|---|----------|
| RECEIVED INTERNATIONAL EXAMINING AUTHORITY | |
| RECEIVE PCT OCT 20 1999 | |
| NOTIFICATION OF TRANSMISSION OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1) | |
| Date of mailing (day/month/year) | 13.10.99 |

| | | |
|---|--|--|
| Applicant's or agent's file reference 75844 | IMPORTANT NOTIFICATION | |
| International application No. PCT/US98/10685 | International filing date (day/month/year) 27/05/1998 | Priority date (day/month/year) 27/05/1997 |
| Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA, re | | |

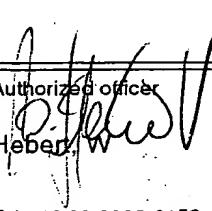
1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

| | |
|---|---|
| Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer  Heber W. Tel. +49 89 2399-2152 |
|---|---|



PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

| | | |
|--|--|--|
| Applicant's or agent's file reference 75844 | FOR FURTHER ACTION | |
| See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | | |
| International application No. PCT/US98/10685 | International filing date (day/month/year) 27/05/1998 | Priority date (day/month/year) 27/05/1997 |
| International Patent Classification (IPC) or national classification and IPC A61K33/00 | | |
| Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA, re | | |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 1 sheets.</p> | | |
| <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application | | |

| | |
|--|--|
| Date of submission of the demand 18/12/1998 | Date of completion of this report 13.10.99 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Iserl, B Telephone No. +49 89 2399 8691 |



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/10685

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1,3-17 as originally filed

2 as received on 20/08/1999 with letter of 20/08/1999

Claims, No.:

1-27 as originally filed

Drawings, sheets:

1/2,2/2 as originally filed

2. The amendments have resulted in the cancellation of:

- the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application.
 claims Nos. 1-27 in part.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/10685

because:

- the said international application, or the said claims Nos. 1-27 (for industrial applicability) relate to the following subject-matter which does not require an international preliminary examination (*specify*):
see separate sheet
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. 1-27 in part.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | |
|-------------------------------|------------------|
| Novelty (N) | Yes: Claims 1-27 |
| | No: Claims |
| Inventive step (IS) | Yes: Claims |
| | No: Claims 1-27 |
| Industrial applicability (IA) | Yes: Claims 1-27 |
| | No: Claims |

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/10685

SECTION III

Claims 1-27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V:

- 1). The present report solely concerns the use of the compound Tempol in accordance with the worked examples, and the general idea underlying the application that is the use of nitroxide in the treatment of cancer. See also Box III (Sheets 1-2), and the International search report.

- 2). Prior art

The following documents (D) cited in the International search report are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 = PAACR ANNUAL MEETING, vol. 36, no. 0, 1995, page 387
D2 = PAACR ANNUAL MEETING, vol. 38, no. 0, March 1977, page 193
D3 = PAACR ANNUAL MEETING, vol. 39, no. 0, March 1998, page 90
D4 = WO -A- 96 40127

Unless indicated otherwise reference is made to the relevant passages emphasized in the search report.

- 2.1 D3 is an intermediate document which represents the scientific disclosure of the subject- matter of the present application.

- 3). Novelty:

The subject-matter of the present claims 1-27 is considered novel.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/10685

The claims 1-27 relate to the use of nitroxide or a prodrug thereof in the treatment of cancer. D1 and D2 differ therefrom basically in that they describe cytotoxic effects of the presently preferred piperidine nitroxide Tempol against cancer cells in vitro.

4). Inventive step:

The subject-matter of claims 1-27 is not considered inventive:

The present application relates to the prophylactic and therapeutic treatment of cancer in animals.

On the basis of D1 and D2, which show chemotherapeutic efficacy of Tempol in vitro, the problem of the present application could be to identify possible conditions bringing about an anticancer effect in vivo. As shown in the examples of the present application, the development of cancer could be prevented by continuous oral prophylactic administration of Tempol. This particular finding is considered non-obvious from the prior art.

It is noted that the scope of the present claims includes therapeutic cancer treatment as well as various modes/schemes of administration. However, there is no indication in the application which justifies a generalisation of the working examples in this respect. Moreover it appears, that a skilled artisan would expect an anticancer effect of Tempol in vivo, e.g., after administration of high doses, as the prior art does not differentiate between in vitro and in vivo effects of nitroxides, either. See page 2, line 18 - page 3, line 7 of the application.

5). Industrial applicability:

For the assessment of the present claims 1-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/10685

dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VIII

- 6). It is apparently not clear from the description, which cancers originate from a defect of the p53 gene (claims 23,25,27).

tumorigenesis (Srivastava et al., Nature 348: 747-749 (1990)). The p53 protein also plays a role in the cellular response to DNA-damaging agents by facilitating a block in the G1 phase of the cell cycle following DNA damage, thereby providing time for repair of the DNA damage (Pietenpol et al., Nature 365: 17-18 (1993); and Kuerbitz et al., PNAS USA 89: 7491-7495 (1992)) or by causing apoptosis (Yonish-Rouach et al., Nature 352: 345-347 (1991)).

In order to enable the further study of the p53 gene, recombinant DNA techniques have been used to develop rodent models. In one model, the rodents are homozygous for mutant p53 alleles ($p53^{--}$), such that the p53 gene is disrupted or "knocked-out" ($p53^{-/-}$) and does not function, and the rodents are highly susceptible at an early age to a variety of tumors (Donehower et al., Nature 356: 251-221 (1992)). In another model, the rodents are heterozygous for wild-type and mutant p53 alleles ($p53^{+/-}$) and, although they develop tumors 10-20 months after birth, they live considerably longer than the homozygous mutant p53 rodents (Harvey et al., Nature/Genetics 5: 225-229 (1993)). Exposure of these rodents to carcinogens, such as dimethylnitrosamine, or whole body irradiation accelerates tumor formation (Harvey et al. (1993), *supra*; and Lee et al., Oncogene 12: 3731-3736 (1994)).

Nitroxides are stable compounds, which are low in molecular weight, metal-independent, nontoxic and nonallergenic, and are characterized by low reactivity with oxygen, high solubility in aqueous solutions, and the ability to cross cellular membranes. The lipophilicity of nitroxides can be controlled by the addition of various organic substituents, in order to facilitate the targeting of the nitroxides to specific organs or organelles.

Nitroxides have been shown to protect cells and animals against the untoward acute effects, such as cytotoxicity, of short-term exposure to lethal doses of free radicals and oxidative species, such as superoxide, hydrogen peroxide, hydroxyl radicals, and hydroperoxides, i.e., by functioning as antioxidants (U.S. Patent No. 5,462,946). In cell culture, nitroxides have been shown to sensitize hypoxic cells to ionizing radiation and, paradoxically, protect aerobic cells from ionizing radiation. Also in cell culture, nitroxides have been shown to protect cells against the acute cytotoxic affects of paraquat and anti-neoplastic agents. Tempol, a nitroxide, has been shown to be cytotoxic against neoplastic cell lines *in vitro* (Monti et al., PAACR, 36: 387 (1995), and Monti et al., PAACR, 38: 193 (1997)). In animals, nitroxides have